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For the Patent- and Registration Office

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NOVEL COMPOUNDS

The present invention relates to novel imidazo and thiazolopyridine compounds which are JAK3 Kinase inhibitors, methods for their preparation, intermediates and pharmaceutical compositions comprising them.

Janus Kinase 3 (JAK3) is a member of the Janus family of protein kinases. Although the other members of this family are expressed by essentially all tissues, JAK3 expression is limited to hematopoietic cells. This is consistent with its essential role in signaling through the receptors for IL-2, IL-4, IL-7, IL-9, IL-13 and IL-15 by non-covalent association of JAK3 with the gamma chain common to these multichain receptors. These cytokines all have a shared function in that they are involved in lymphocyte differentiation and proliferation. XSCID patient populations have been identified with severely reduced levels of JAK3 protein or with genetic defects to the common gamma chain, suggesting that immunosuppression should result from blocking signaling through the JAK3 pathway. Animal studies have suggested that JAK3 not only play a critical role in B- and T-lymphocyte maturation, but that JAK3 is constitutively required to maintain T-cell function. Modulation of immune activity through this novel mechanism can prove useful in the treatment of T-cell proliferative disorders such as transplant rejection and autoimmune diseases.

The role of JAK3 in mast cells has been described in knockout mice. Thus, IgE/antigen induced degranulation and mediator release were substantially reduced in mast cells generated from JAK3 deficient mice. JAK3 deficiency does not affect mast cell proliferation in vitro, it has also been shown that IgE receptor levels and mediator contents are identical in JAK3^{-/-} and JAK3^{+/+} mast cells. Therefore, JAK3 appears essential for the complete response of IgE challenged mast cells. The role of JAK3 in mast cell activation has been well established in murine system, however, there is no published data on mast cell function in the AR-SCID patients. Targeting JAK3 provides the basis for new and effective treatment of mast cell mediated allergic reactions.

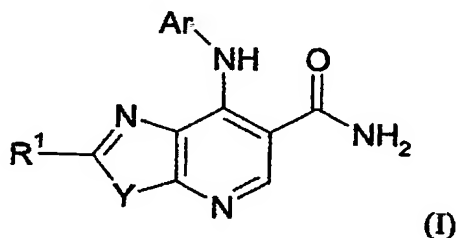
To date a number of JAK3 inhibitors has been disclosed, among them are quinazolines (Sudbeck, E. A. et al. Clinical Cancer Res. 5(1999)1569-82, WO 00/0202) and pyrrolo[2,3-d]pyrimidines (Blumenkopf, T. A. et al. WO 99/65909).

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In the current application compounds, 4-anilinoquinoline-3-carboxamides, are claimed as JAK3 inhibitors. Structurally related compounds have previously been described as kinase inhibitors e.g. WO 00/18761 and WO 98/43960 disclose substituted quinoline-3-carbonitrile derivatives. In a recent publication (Boschelli, D.H. et al. J. Med. Chem. 44(2001)822-33) one compound of the present invention has proved not to have any inhibitory capacity towards the activity of the protein tyrosine kinase Src. JAK3 is not mentioned in any of the above literature examples.

WO 02/092571 discloses a series of quinoline derivatives for use in the treatment of a disease mediated by JAK3.

There is a need for further compounds having this activity, and therefore the present invention provides a compound of formula (I):



wherein:

Y is NH, S or O;

R¹ is phenyl or a 5- to 7-membered heteroaromatic ring containing 1 to 3 heteroatoms, each of which is optionally substituted by one or more groups selected from C₁-C₈ alkyl, C₁-C₈ alkoxy, S(O)_nC₁-C₈ alkyl or a group -R²-(CH₂)_p-R³;

n is 0, 1 or 2;

R² is a bond, NH, NC₁-C₈ alkyl, S or O;

p is 0 - 3;

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R^3 is NR^4R^5 where R^4 and R^5 are independently hydrogen or C_1 - C_8 alkyl, or R^3 is a phenyl ring, a 5 to 7-membered saturated ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulphur, or a 5- to 7-membered heteroaryl group containing 1 to 3 heteroatoms selected from nitrogen oxygen and sulphur, each of which can optionally substituted by one or more groups selected from $CONR^4R^5$, NR^4R^5 , C_1 - C_8 alkyl, C_1 - C_8 alkoxy, $S(O)_n C_1$ - C_8 alkyl, hydroxyl, CN, halogen, $NHCOC_1$ - C_8 alkyl, R^2 -(CH_2)_p-OH or morpholine;

n is 1 to 4;

Ar is phenyl which can be optionally substituted by one or more groups selected from halogen, hydroxy, cyano, C_1 - C_8 alkyl (itself optionally substituted by one or more hydroxy or cyano groups or fluorine atoms), CH_2 - R^6 ; $CH_2O(CH_2)_n OC_{1-6}$ alkyl, C_1 - C_8 alkyl- NR^3 - R^4 , or a C_{2-6} alkyl chain optionally containing an NR^7 group in the chain and optionally substituted by one or more OH groups and optionally terminating in a cycloalkyl or phenyl group, the cycloalkyl and phenyl groups themselves being optionally substituted by one or more hydroxyl groups;

R^6 is a 5 to 7-membered saturated ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulphur, an aryl or 5- to 7-membered heteroaryl group containing 1 to 3 heteroatoms selected from nitrogen oxygen and sulphur, each of which can optionally substituted by one or more substituents selected from hydroxyl or hydroxymethyl;

R^7 is hydrogen or C_{1-6} alkyl;

and pharmaceutically acceptable salts thereof.

The term alkyl, whether used alone or as part of another group such as alkoxy, means any straight or branched chained alkyl group. The term aryl includes phenyl and naphthyl groups. Compounds of the present invention include all stereoisomers, pure and mixed racemates, and mixtures thereof. Tautomers of compounds of formula (I) also form an aspect of the invention.

Preferably Y is NH or S.

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Preferably R^1 is by SCH_3 , $SOCH_3$, $O-Ph-CONH_2$, $O(CH_2)_3-N(CH_3)NH(CH_2)_3$ -morpholine, $O(CH_2)_2$ -morpholine, OCH_3 , $O(CH_2)_2-N(CH_3)_2$, 2-(3-aminophenoxy), 4-methoxyphenoxy, or pyridyl or phenyl optionally substituted by OH, $N(CH_3)_2$, OCH_3 , CN, fluoro, chloro, $S(O)_2CH_3$, $NHCOCH_3$, $O(CH_2)_2OH$, $N(CH_3)(CH_2)_2OH$, morpholine or $O(CH_2)_2-OH$

When R^2 is a 5 to 7-membered saturated ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulphur suitable examples include morpholine, thiomorpholine, azetidine, imidazolidine, pyrrolidine, piperidine and piperazine.

When R^2 is a 5- to 7-membered heteroaryl group containing 1 to 3 heteroatoms selected from nitrogen oxygen and sulphur, examples include pyridine, pyrimidine, thiazole, oxazole, pyrazole, imidazole, furan, isoxazole, pyrrole.

Preferably Ar is phenyl which can be optionally substituted by those substituent groups of the examples herein. Especially preferred substituents include one or more substituents, which can be the same or different, selected from hydroxymethyl, ethyl, [(2-hydroxypropyl)amino]methyl, [(2-hydroxy-1-methylethyl)amino]methyl, (1H-imidazol-1-ylmethyl), [(2,3-dihydroxypropyl)amino]methyl, 3-(morpholin-4-ylmethyl), {[2-cyclohexyl-1-(hydroxymethyl)ethyl]amino}methyl, {[1-benzyl-2-hydroxyethyl]amino}methyl, (3-hydroxypyrrolidin-1-yl)methyl, {[2-hydroxy-1-phenylethyl]amino}methyl, {(2-hydroxy-1-(hydroxymethyl)-2-phenylethyl)amino}methyl, {(2-hydroxycyclohexyl)amino}methyl, {(2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino}methyl, 3-hydroxypiperidin-1-ylmethyl, {[1-(hydroxymethyl)-2-methylpropyl]amino}methyl, {[4-(methylsulphonyl)benzyl]amino}methyl, and {[2-(3,4-dihydroxyphenyl)-2-hydroxyethyl]amino}methyl.

Substituents can be present on any suitable position of the Ar group. More than one substituent can be present, and these can be the same or different. One or two substituent groups are preferred.

Especially preferred compounds of the invention include those exemplified herein, both in free base form and as pharmaceutically acceptable salts.

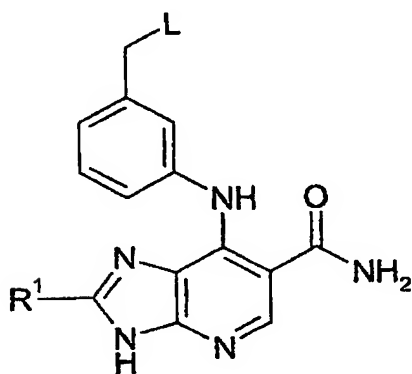
Compounds of the invention can form pharmaceutically acceptable solvates and salts. The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic,

phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, trifluoroacetic and methanesulphonic acids.

The invention also provides a method of treating or preventing a disease mediated by JAK3 which comprises administering to a mammal a compound of formula (I) as defined above.

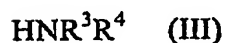
In a further aspect the invention provides a process for the preparation of a compound of formula (I) which comprises:

- (a) for compounds of formula (I) where Y is NH and Ar is phenyl substituted by $\text{CH}_2\text{NR}^3\text{R}^4$, reaction of a compound of formula (II):



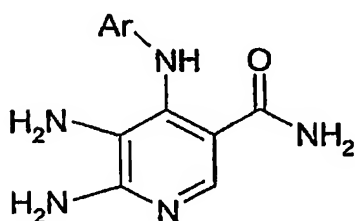
(II)

in which R^1 is as defined in formula (I) or is a protected derivative thereof and L is a leaving group, with a compound of formula (III):



in which R^3 and R^4 are as defined in formula (I) or are protected derivatives thereof, or

- (b) for compounds of formula (I) where Y is NH, reaction of a compound of formula (IV):



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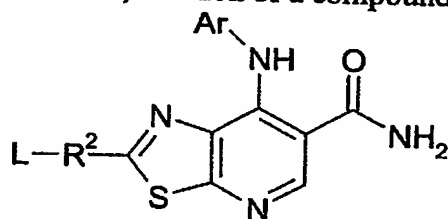
(IV)

in which Ar is as defined in formula (I) or is a protected derivative thereof, with a
5 compound of formula (V):



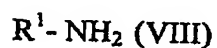
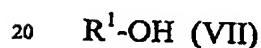
10 in which R^1 is as defined in formula (I) or is a protected derivative thereof, or

(c) for compounds of formula (I) where Y is S and R^1 is a group $-R^2-(CH_2)_p-R^3$ where R^2 is O or NH, reaction of a compound of formula (VI):



15 (VI)

in which Ar is as defined in formula (I) or is a protected derivative thereof, R^2 is O or NH, and L is a leaving group, with a compound of formula (VII) or (VIII):



25 in which R^1 is as defined in formula (I) or is a protected derivative thereof

and optionally thereafter any of the above processes:

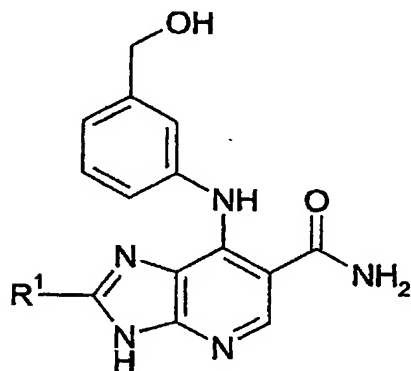
- removing any protecting groups
- converting a compound of formula (I) into a further compound of formula (I)
- forming a pharmaceutically acceptable salt.

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Compounds of formula (I) can be converted into further compounds of formula (I) using standard chemistry.

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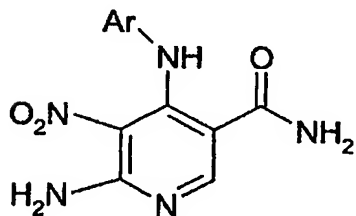
Reaction of compounds (II) and (III) can be carried out in the presence of DIPA in a solvent such as NMP. Preferably the leaving group L is halogen, especially chloro. Compounds of formula (II) can be prepared by reacting compounds of formula (IX):



(IX)

in which R¹ is as defined in formula (II) with a chlorinating agent such as SOCl₂ in dichloromethane.

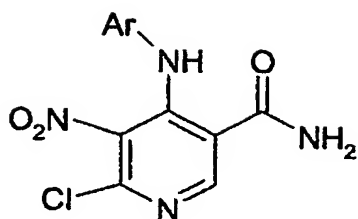
Reaction of compounds of formula (IV) and (V) can be carried out in a solvent such as DMF at elevated temperature, for example at about 120°C in the presence of an oxidant such as FeCl₃. Compounds of formula (IV) can be prepared from compounds of formula (X):



(X)

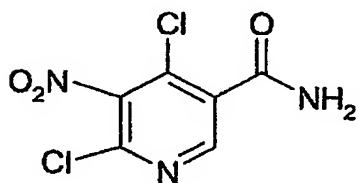
in which Ar is as defined in formula (IV) by hydrogenation using a palladium catalyst in a protic solvent such as methanol. Compounds of formula (X) can be prepared from compounds of formula (XI):

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(XI)

- 5 in which Ar is as defined in formula (IV) by treatment with ammonia. Compounds of formula (XI) can be prepared from compounds of formula (XII):

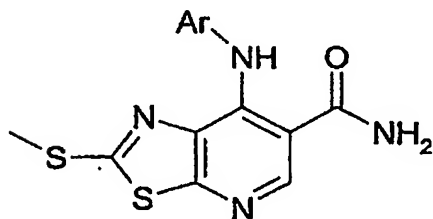


10 (XII)

by reaction with an amine Ar-NH₂ in which Ar is as defined in formula (IV) in an aprotic solvent such as DMF at elevated temperature.

- 15 Reaction of compounds (VI) with (VII) or (VIII) can be carried out in the presence of a suitable base at ambient or elevated temperatures. Suitable leaving groups for compounds (VI) include SO₂Me and SMe.

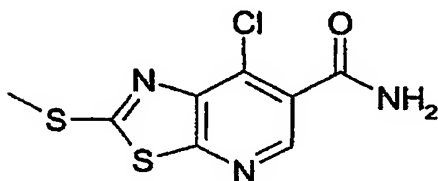
- 20 Compounds of formula (VI) can be prepared by oxidation of the corresponding sulphur compound (XIII):



(XIII)

using a reagent such as 3-chloroperbenzoic acid to give the sulfoxide or potassium permanganate to give the sulphone.

Compounds of formula (XIII) are prepared from compounds of formula (XIV):



(XIV)

by reacting with an amine Ar-NH_2 .

It will be appreciated that certain functional groups may need to be protected using standard protecting groups. The protection and deprotection of functional groups is for example, described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 3rd edition, T. W. Greene & P. G. M. Wuts, Wiley-Interscience (1999).

Diseases mediated by JAK3 include inflammatory, immunological, and bronchopulmonary disorders.

20

The present invention also relates to a pharmaceutical composition for (a) treating or preventing a disorder or condition selected from organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, rhinitis, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia, and other autoimmune diseases or (b) the inhibition of protein tyrosine kinases or Janus kinase 3 (JAK3) in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof, effective in such disorders or conditions and a pharmaceutically acceptable carrier.

30

Preferably the compounds of the invention are used for the treatment of asthma, rheumatoid arthritis, and host versus graft rejection/transplantation.

ABSTRACT

The present invention also relates to a pharmaceutical composition for (a) treating or preventing a disorder or condition selected from organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cane, asthma, rhinitis, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia, and other autoimmune diseases or (b) the inhibition of protein tyrosine kinases or Janus kinase 3 (JAK3) in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof, alone or in combination with a T-cell immunosuppressant or anti-inflammatory agents, effective in such disorders or conditions and a pharmaceutically acceptable carrier.

The present invention also relates to a method for the inhibition of protein tyrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

In a still further aspect the invention provides the use of a compound of formula (IA) as a therapeutic agent.

The dose of the compound to be administered will depend on the relevant indication, the age, weight and sex of the patient and may be determined by a physician. The dosage will preferably be in the range of from 0.1 mg/kg to 100 mg/kg.

The compounds may be administered topically, e.g. to the lung and/or the airways, in the form of solutions, suspensions, HFA aerosols or dry powder formulations, e.g. formulations in the inhaler device known as the Turbuhaler®; or systemically, e.g. by oral administration in the form of tablets, pills, capsules, syrups, powders or granules, or by parenteral administration, e.g. in the form of sterile parenteral solutions or suspensions, or by rectal administration, e.g. in the form of suppositories.

The compounds of the invention may be administered on their own or as a pharmaceutical composition comprising the compound of the invention in combination with a pharmaceutically acceptable diluent, adjuvant or carrier. Particularly preferred are compositions not containing material capable of causing an adverse, e.g. an allergic, reaction.

Dry powder formulations and pressurized HFA aerosols of the compounds of the invention may be administered by oral or nasal inhalation. For inhalation the compound is desirably finely divided. The finely divided compound preferably has a mass median diameter of less than 10 μm , and may be suspended in a propellant mixture with the assistance of a dispersant, such as a $\text{C}_8\text{-C}_{20}$ fatty acid or salt thereof, (e.g. oleic acid), a bile salt, a phospholipid, an alkyl saccharide, a perfluorinated or polyethoxylated surfactant, or other pharmaceutically acceptable dispersant.

The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

One possibility is to mix the finely divided compound with a carrier substance, e.g. a mono-, di- or polysaccharide, a sugar alcohol, or an other polyol. Suitable carriers are sugars, e.g. lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol; and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, e.g. that known as the Turbuhaler[®] in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active compound, with or without a carrier substance, is delivered to the patient.

For oral administration the active compound may be admixed with an adjuvant or a carrier, e.g. lactose, saccharose, sorbitol, mannitol; a starch, e.g. potato starch, corn starch or amylopectin; a cellulose derivative; a binder, e.g. gelatine or polyvinylpyrrolidone, and/or a lubricant, e.g. magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

For the preparation of soft gelatine capsules, the compound may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the

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compound using either the above mentioned excipients for tablets. Also liquid or semisolid formulations of the drug may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing the compound, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

The compounds of the invention may also be administered in conjunction with other compounds used for the treatment of the above conditions.

The term 'medical therapy' as used herein is intended to include prophylactic, diagnostic and therapeutic regimens carried out in vivo or ex vivo on humans or other mammals.

The following Examples illustrate the invention.

General methods All reactions were performed in dried glassware in an argon atmosphere at room temperature, unless otherwise noted. All solvents and reagents and solvents were used as received. Merck Silica gel 60 (0.040-0.063 mm) was used for preparative silica gel chromatography. A Kromasil KR-100-5-C18 column (250 x 20 mm, Akzo Nobel) and mixtures of acetonitrile/water at a flow rate of 10 ml/min was used for preparative HPLC. Reactions were monitored at 254 nm by analytical HPLC, using a Kromasil C-18 column (150 x 4.6 mm) and a gradient (containing 0.1% trifluoroacetic acid) of 5 to 100% of acetonitrile in water at a flow rate of 1 ml/min. Evaporations of solvents were performed under reduced pressure using a rotary evaporator at a maximum temperature of 40°C. Products were dried under reduced pressure at 40 °C.

¹H-NMR spectra were recorded on a Varian Inova-400 or Unity-500+ instrument. The central solvent peak of chloroform-*d* (δ 7.27 ppm), dimethylsulfoxide-*d*₆ (δ 2.50 ppm) or methanol-*d*₄ (δ 3.35 ppm) were used as internal references. Low resolution mass spectra obtained on a Hewlett Packard 1100 LC-MS system equipped with a APCI ionisation chamber.

Merck Silica gel 60 (0.040-0.063 mm) was used for preparative silica gel chromatography. A Kromasil KR-100-5-C18 column (250 x 20 mm, Akzo Nobel) and mixtures of acetonitrile/water at a flow rate of 10 ml/min was used for preparative HPLC. Reactions

were monitored at 254 nm by analytical HPLC, using a Kromasil C-18 column (150 x 4.6 mm) and a gradient (containing 0.1% trifluoroacetic acid) of 5 to 100% of acetonitrile in water at a flow rate of 1 ml/min. Evaporations of solvents were performed under reduced pressure using a rotary evaporator at a maximum temperature of 40 °C. Products were

Thiazolopyridines

Example 1

10 7-[(2-Ethylphenyl)amino]-2-methoxy[1,3]thiazolo[5,4-b]pyridine-6-carboxamide

1a) 7-Hydroxy-2-(methylthio)[1,3]thiazolo[5,4-b]pyridine-6-carboxylic acid

The title compound was synthesized according to procedure described by D.C. Leysen; A. Haemers; W. Bollaert, *J. Heterocyclic Chem.* 1984, 21, 401.

15 1b) 7-Chloro-2-(methylthio)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide

To a suspension of finely grinded 1a (3.70 g, 15.3 mmol) in thionyl chloride (100 mL) was added a drop of DMF. The suspension was stirred at 50 °C for 4h. The thionyl chloride was evaporated. Toluene was added. After a short time of stirring the toluene was evaporated. Acetone (125 mL) was added to the crude residue to form a suspension which was stirred and cooled to 0 °C. Cold Ammonium hydroxide (25%, 20 mL, 306 mmol) was added and the reaction was stirred for 1h and put in a refrigerator over night. The precipitate was filtered off and washed twice with water and dried under vacuum at 70 °C over night. Yield: 2.86g (72%).

25 ¹H NMR (400 MHz, DMSO-d₆): δ 8.52 (s, 1H), 8.14 (s, 1H), 7.91 (s, 1H), 2.85 (s, 3H). APCI-MS m/z: 259.9 [MH⁺].

1c) 7-[(2-Ethylphenyl)amino]-2-(methylthio)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide

30 To a solution of 1b (2.00 g, 7.7 mmol) and 2-ethylaniline (2.9 mL, 23.1 mmol) in DMSO (30 mL) was added BF₃·OEt₂ (0.95mL, 7.7 mmol). The solution was stirred over night at 110 °C. After cooling the reaction was poured into ice water and EtOAc. sodium carbonate (5 %) was added to obtain an alkaline solution. The organic phase was separated and the water phase extracted twice with EtOAc. The combined organic phases were washed with

three portions of water and brine. Dried over sodium sulphate and purified by flash chromatography (toluene:EtOAc 1:1).

Yield 1.98g, 5.75 mmol (75%).

¹H NMR (400 MHz, DMSO-d₆) δ 10.99 (s, 1H), 8.67 (s, 1H), 8.31 (s, 1H), 7.70 (s, 1H), 7.27 - 7.25 (m, 1H), 7.16 - 7.13 (m, 2H), 7.09 - 7.07 (m, 1H), 2.58 (q, *J* = 7.5 Hz, 2H), 2.16 (s, 3H), 1.13 (t, *J* = 7.5 Hz, 3H).

APCI-MS *m/z*: 345.2 [MH⁺].

10 **1d 7-[(2-Ethylphenyl)amino]-2-(methylsulfinyl)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide**

A suspension of **1c** (1.00 g, 2.91 mmol) stirred in dichloromethane (15 mL) was cooled to -15 °C. 3-Chloroperbenzoic acid (680 mg, 3.05 mmol) was added portion wise. The reaction was stirred 1h, allowed to reach room temperature and quenched with sodium thiosulfate (5 %). The organic phase was separated, washed with sodium bicarbonate and brine and dried over sodium sulphate. The product was purified by flash chromatography (EtOAc as eluent).

Yield: 910 mg, 2.52 mmol (87%).

¹H NMR (400 MHz, DMSO-d₆) δ 11.28 (s, 1H), 8.84 (s, 1H), 8.40 (s, 1H), 7.78 (s, 1H), 7.27 - 7.26 (m, 1H), 7.20 - 7.15 (m, 1H), 7.14 - 7.10 (m, 2H), 2.70 (s, 3H), 2.57 (q, *J* = 7.4 Hz, 2H), 1.11 (t, *J* = 7.6 Hz, 3H).

APCI-MS *M/Z*: 361.1 [MH⁺].

1e 7-[(2-Ethylphenyl)amino]-2-(methylsulfonyl)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide

Compound **1d** (600 mg, 1.74 mmol) was dissolved in HOAc (16 mL). The solution was cooled in an ice bath. When the solution started to freeze a slow addition of potassium permanganate (560 mg, 3.52 mmol) dissolved in water (12 mL) was started. After 20 min the addition was completed. The stirring was continued for an additional 30 min. A saturated solution of sodium bisulphite (2.0 mL) was added. A precipitate was formed. The suspension was centrifuged and the supernatant was collected and extracted with chloroform. The organic layer was separated, washed twice with sodium bicarbonate (5%) and brine, and dried over sodium sulphate. The product was purified by flash-chromatography (toluene: EtOAc 4:6).

Yield: 101 mg (15%).

APCI-MS *m/z*: 377.2 [MH⁺].

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1f) 7-[(2-Ethylphenyl)amino]-2-methoxy[1,3]thiazolo[5,4-b]pyridine-6-carboxamide 1e (20 mg, 0.052 mmol) was placed in a dry reaction flask. Sodium methoxide (0.35M in methanol, 0.16 mL, 560 μ mol) was added. The reaction was stirred at room temperature for 2h and then quenched by adding water. The mixture was extracted with chloroform.

5 The organic layer was separated and washed twice with water and dried over sodium sulphate. The product was purified by flash chromatography (toluene:EtOAc 1:1).

Yield: 10 mg (59%).

¹H NMR (400 MHz, DMSO-d₆) δ 10.79 (s, 1H), 8.62 (s, 1H), 8.28 (s, 1H), 7.67 (s, 1H), 7.23 (dd, J = 7.2, 1.9 Hz, 1H), 7.12 (qd, J = 7.3, 5.4 Hz, 2H), 7.02 (dd, J = 7.3, 1.7 Hz, 1H), 3.60 (s, 3H), 2.59 (q, J = 7.8 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H).

10 APCI-MS m/z : 329.2 [MH⁺].

Example 2

15 7-[(2-methylphenyl)amino]-2-(methylthio)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide trifluoroacetate

The title compound was prepared in an analogous way to 1c (100 mg, 0.38 mmol), 2-methylaniline (0.123 mL, 1.15 mmol) and boron trifluoride ethyl etherate (0.047 mL, 0.38 mmol) in DMSO (2 mL). The product was purified by prep-HPLC.

20 Yield: 17 mg, 0.038 mmol (10%).

APCI-MS m/z : 331.2 [MH⁺]

Example 3

25 7-[(3-(hydroxymethyl)-2-methylphenyl)amino]-2-(methylthio)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide trifluoroacetate

The title compound was prepared in an analogous way to 1c (100 mg, 0.38 mmol), 3-(hydroxymethyl)-2-methylaniline (158 mg, 1.15 mmol) and boron trifluoride ethyl etherate (0.047 mL, 0.38 mmol) in dmso (2 mL). The product was purified by prep-HPLC.

Yield: 53 mg, 0.11 mmol (29%).

30 APCI-MS m/z : 361.2 [MH⁺]

Example 4-7 were prepared in an analogous way to 1f.

Example 4

35 2-[2-(Dimethylamino)ethoxy]-7-[(2-ethylphenyl)amino][1,3]thiazolo[5,4-b]pyridine-6-carboxamide

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APCI-MS m/z: 386.2 [MH+].

Example 5

2-[3-(Dimethylamino)propoxy]-7-[(2-ethylphenyl)amino][1,3]thiazolo[5,4-b]pyridine-6-carboxamide

APCI-MS m/z: 400.2 [MH+].

Example 6

7-[(2-Ethylphenyl)amino]-2-(2-morpholin-4-ylethoxy)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide

APCI-MS m/z: 428.2 [MH+].

Example 7

7-[(2-Ethylphenyl)amino]-2-[(3-morpholin-4-ylpropyl)amino][1,3]thiazolo[5,4-b]pyridine-6-carboxamide

APCI-MS m/z: 441.2 [MH+].

Example 8-10 were prepared in an analogous way to example 1f using 1d as reactant and at slightly elevated temperature (50°C).

Example 8

2-[4-(Aminocarbonyl)phenoxy]-7-[(2-ethylphenyl)amino][1,3]thiazolo[5,4-b]pyridine-6-carboxamide

APCI-MS m/z: 434.1 [MH+].

Example 9

2-(3-aminophenoxy)-7-[(2-ethylphenyl)amino][1,3]thiazolo[5,4-b]pyridine-6-carboxamide bis(trifluoroacetate)

APCI-MS m/z: 406.1 [MH+].

Example 10

7-[(2-ethylphenyl)amino]-2-(4-methoxyphenoxy)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide trifluoroacetate

APCI-MS m/z: 421.1 [MH+].

Imidazopyridines

Example 1

5 **7-{{2-ethyl-3-(hydroxymethyl)phenyl}amino}-2-phenyl-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate (salt)**

1a) Methyl 4,6-dichloro-5-nitronicotinate

The title compound was prepared according to the protocol of J. P. Sanchez and R. D. Gogliottias, *J. Heterocyclic Chem.* 1993, 30, 855-859.

1b) Methyl 6-chloro-4-{{2-ethyl-3-(hydroxymethyl)phenyl}amino}-5-nitronicotinate A solution of Methyl 4,6-dichloro-5-nitronicotinate (603 mg, 2.40 mmol), 2-Ethyl-3-hydroxymethyl-aniline (363 mg, 2.40 mmol, 1.0 equiv.) and ethyl(diisopropyl)amine (373 mg, 2.88 mmol, 1.2 equiv.) was stirred at 50 °C over night. Addition of water, extraction with ethylacetate followed by washing with brine and drying over sodium sulfate resulted in a crude product. After chromatography on silica gel [methyl(*tert*-butyl)ether/heptane = 4:1] 466 mg of the title compound were obtained as a yellow solid. ¹H-NMR (400MHz, CDCl₃): δ 10.37 (s, 1H), 8.85 (s, 1H), 7.39 (d, *J* 7.1Hz, 1H), 7.14 (t, *J* 7.9Hz, 1H), 6.97 (d, *J* 7.7Hz, 1H), 4.76 (s, 2H), 4.00 (s, 3H), 2.75 (q, *J* 7.5Hz, 2H), 1.22 (t, *J* = 7.7Hz, 3H).

1c) 6-Amino-4-{{2-ethyl-3-(hydroxymethyl)phenyl}amino}-5-nitronicotinamide

The reaction was carried out in a sealed steel tube equipped with a glass inlet. Compound 1b (436 mg, 1.19 mmol) was placed in the reaction vessel and liquid ammonia was condensed in at -78°C. Then the mixture was allowed to warm up to room temperature. With a delay of 12 h the reaction mixture was warmed up to 80°C for additional 8 h. Then the reaction vessel was cooled down to -78°C, opened and ammonia was allowed to evaporate. Filtration of the crude on silica gel (EtOAc/Aceton = 9:1) afforded 239 mg (61%) of the pure title compound as a yellow solid. ¹H-NMR (400MHz, DMSO-d₆): δ 11.84 (s, 1H), 8.49 (s, 1H), 8.10 (s, 1H), 7.49 (s, 1H), 7.39 (s, 2H), 7.13 (d, *J* 7.0Hz, 1H), 6.98 (t, *J* 7.8Hz, 1H), 6.69 (d, *J* 7.3Hz, 1H), 5.14 (t, *J* 5.5Hz, 1H), 4.54 (d, *J* 5.5Hz, 2H), 2.64 (q, *J* 7.5Hz, 2H), 1.14 (t, *J* 7.3Hz, 3H).

1d) 5,6-Diamino-4-{{2-ethyl-3-(hydroxymethyl)phenyl}amino}nicotinamide

Compound 1c (2.22g, 6.71 mmol) was dissolved in methanol (40 ml) and palladium (10%

on charcoal, 450 mg) was added. The mixture was stirred under normal pressure under a hydrogen atmosphere at room temperature over night. Filtration over celite and evaporation of the solvent resulted in the title compound as a colourless solid in quantitative yields.

5 ¹H-NMR (400MHz, DMSO-d₆): δ 9.17 (s, 1H), 7.88 (s, 1H), 7.80 (s, 1H), 7.14 (s, 1H), 6.98 (t, *J* 7.7Hz, 1H), 6.92 (d, *J* 6.7Hz, 1H), 6.16 (d, *J* 7.4Hz, 1H), 5.90 (s, 2H), 5.03 (t, *J* 5.1Hz, 1H), 4.53 (d, *J* 4.9Hz, 2H), 3.72 (s, 2H), 2.72 (q, *J* = 7.5Hz, 2H), 1.21 (t, *J* 7.4Hz, 3H).

APCI-MS: *m/z* 302.2 [MH⁺].

10

1e) 7-[[2-ethyl-3-(hydroxymethyl)phenyl]amino]-2-phenyl-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate (salt) A solution of compound 1d (18 mg, 59.0 μmol), benzaldehyde (7mg, 6.6 μL, 66.0 μmol, 1.1 equiv.) and a catalytic amount of *p*-toluensulfonic acid monohydrate in DMF (400μL) was stirred at 120°C for 1h. After cooling down the mixture was diluted with acetonitrile (2.5 mL) and water (2mL) and subjected to a reversed phase HPLC. After freeze-drying 8 mg (27 %) of the title compound as its corresponding trifluoroacetate were obtained as a white powder. The NMR was recorded from the neutralized product.

15

20 ¹H-NMR (400MHz, DMSO-d₆): δ 13.30 (s, 1H), 11.13 (s, 1H), 8.59 (s, 1H), 8.10 (s, 1H), 7.40 (m, 3H), 7.67 (m, 1H), 7.40 (m, 3H), 7.18 (m, 2H), 7.09 (t, *J* 7.4Hz, 1H), 5.10 (t, *J* 5.0Hz, 1H), 4.58 (d, *J* 4.7Hz), 2.72 (q, *J* 7.3Hz, 2H), 1.15 (t, *J* 7.2Hz, 3H).

APCI-MS: *m/z* 388.1 [MH⁺].

25

The title compounds of examples 2-26 were prepared according to the procedure described for example 1. In some cases FeCl₃ instead of *p*-toluensulfonic acid was used to catalyze the reaction of step 1e.

7-[(2-ethylphenyl)amino]-2-(4-hydroxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
2-[4-(dimethylamino)phenyl]-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-
30 carboxamide bis(trifluoroacetate)

7-[(2-ethylphenyl)amino]-2-(3-hydroxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
trifluoroacetate (salt)

7-[(2-ethylphenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-
carboxamide trifluoroacetate

- 2-(3,4-dihydroxyphenyl)-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate (salt)
- 2-(3-cyanophenyl)-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
- 5 2-(4-cyanophenyl)-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
- 7-[(2-ethylphenyl)amino]-2-(4-hydroxy-3-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate (salt)
- 2-(3,4-difluorophenyl)-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-
- 10 carboxamide trifluoroacetate
- 2-(3-chloro-4-hydroxyphenyl)-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate (salt)
- 7-[(2-ethylphenyl)amino]-2-(1H-imidazol-4-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide bis(trifluoroacetate)
- 15 7-[(2-ethylphenyl)amino]-2-[4-(methylsulfonyl)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
- 2-[4-(acetylamino)phenyl]-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
- 7-[(2-ethylphenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-
- 20 carboxamide trifluoroacetate (salt)
- 7-[(2-ethylphenyl)amino]-2-{4-[(2-hydroxyethyl)(methyl)amino]phenyl}-3H-imidazo[4,5-b]pyridine-6-carboxamide bis(trifluoroacetate) (salt)
- 7-[(2-ethylphenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide bis(trifluoroacetate)
- 25 7-[(2-ethylphenyl)amino]-2-phenyl-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
- 7-{[2-ethyl-3-(hydroxymethyl)phenyl]amino}-2-(4-hydroxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate (salt)
- 7-{[2-ethyl-3-(hydroxymethyl)phenyl]amino}-2-(4-morpholin-4-ylphenyl)-3H-
- 30 imidazo[4,5-b]pyridine-6-carboxamide

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7-[(2-ethylphenyl)amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
trifluoroacetate

7-[(2-ethylphenyl)amino]-2-pyridin-3-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
trifluoroacetate

5 7-[(2-ethylphenyl)amino]-2-pyridin-2-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
trifluoroacetate

2-[4-(2-{{tert-butyl(diphenyl)silyl}oxy}ethoxy)phenyl]-7-{{2-ethyl-3-
(hydroxymethyl)phenyl}amino}-3H-imidazo[4,5-b]pyridine-6-carboxamide

10 7-{{2-ethyl-3-(hydroxymethyl)phenyl}amino}-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-
6-carboxamide

7-{{2-ethyl-3-(hydroxymethyl)phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-
b]pyridine-6-carboxamide

Example 27

15 7-[(2-ethyl-3-{{(2-hydroxypropyl)amino}methyl}phenyl)amino]-2-(4-methoxyphenyl)-
3H-imidazo[4,5-b]pyridine-6-carboxamide

Treatment of a suspension of example 26 in dichloromethane with thionyl chloride at room
temperature generated the corresponding chloride. The volatiles were removed in vacuo,
20 and the residue was dissolved in NMP. The chloride (0.1M) was then treated with 1.5 eq of
1-amino-propan-2-ol (0.2M in NMP) and 3eq of DIPEA (0.2M in NMP) and heated at 120
°C for 12h generating the title compound in good yield.

25 The title compounds of examples 28-93 were prepared in analogous manner to example
26:

Examples 28 - 93

7-[(2-ethyl-3-{{(2-hydroxypropyl)amino}methyl}phenyl)amino]-2-(4-methoxyphenyl)-3H-
imidazo[4,5-b]pyridine-6-carboxamide

30 7-[(2-ethyl-3-{{(2-hydroxypropyl)amino}methyl}phenyl)amino]-2-[4-(2-
hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethyl-3-{{(2-hydroxy-1-methylethyl)amino}methyl}phenyl)amino]-2-[4-(2-
hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

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7-{{2-ethyl-3-(1H-imidazol-1-ylmethyl)phenyl}amino}-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(3-{{(2,3-dihydroxypropyl)amino}methyl}-2-ethylphenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

5 7-{{2-ethyl-3-(morpholin-4-ylmethyl)phenyl}amino}-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{{3-({[(1S)-2-cyclohexyl-1-(hydroxymethyl)ethyl]amino}methyl)-2-ethylphenyl}amino}-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

10 7-{{3-({[(1S)-1-benzyl-2-hydroxyethyl]amino}methyl)-2-ethylphenyl}amino}-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethyl-3-{{4-(2-hydroxyethyl)piperazin-1-yl}methyl}phenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

15 7-({2-ethyl-3-[(3-hydroxypyrrolidin-1-yl)methyl]phenyl}amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{{2-ethyl-3-({[(1S)-2-hydroxy-1-phenylethyl]amino}methyl)phenyl}amino}-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

20 7-[(2-ethyl-3-{{(2R)-2-(hydroxymethyl)pyrrolidin-1-yl}methyl}phenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{{2-ethyl-3-({[(1S,2S)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino}methyl)phenyl}amino}-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

25 7-[(2-ethyl-3-{{(2-hydroxycyclohexyl)amino}methyl}phenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{{2-ethyl-3-({[(1R,2S)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino}methyl)phenyl}amino}-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

30 7-{{2-ethyl-3-({[(1R,2R)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino}methyl)phenyl}amino}-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-({2-ethyl-3-[(3-hydroxypiperidin-1-yl)methyl]phenyl}amino)-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

35 7-{{2-ethyl-3-({[1-(hydroxymethyl)-2-methylpropyl]amino}methyl)phenyl}amino}-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

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7-{{2-ethyl-3-({[4-(methylsulfonyl)benzyl]amino}methyl)phenyl}amino}-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{{3-({[2-(3,4-dihydroxyphenyl)-2-hydroxyethyl]amino}methyl)-2-ethylphenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

5 7-[(2-ethyl-3-{{(2-hydroxypropyl)amino}methyl}phenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethyl-3-{{(2-hydroxy-1-methylethyl)amino}methyl}phenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

10 7-{{2-ethyl-3-(1H-imidazol-1-ylmethyl)phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate

7-[(3-{{(2,3-dihydroxypropyl)amino}methyl}-2-ethylphenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

15 7-{{2-ethyl-3-(morpholin-4-ylmethyl)phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate

7-{{3-({[(1S)-2-cyclohexyl-1-(hydroxymethyl)ethyl]amino}methyl)-2-ethylphenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{{3-({[(1S)-1-benzyl-2-hydroxyethyl]amino}methyl)-2-ethylphenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

20 7-[(2-ethyl-3-{{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}phenyl}amino)-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{{2-ethyl-3-[(3-hydroxypyrrolidin-1-yl)methyl]phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

25 7-{{2-ethyl-3-({[(1S)-2-hydroxy-1-phenylethyl]amino}methyl)phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethyl-3-{{(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]methyl}phenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

30 7-{{2-ethyl-3-({[(1S,2S)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino}methyl)phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethyl-3-{{(2-hydroxycyclohexyl)amino}methyl}phenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

35 7-{{2-ethyl-3-({[(1R,2S)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino}methyl)phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

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7-{{2-ethyl-3-({[(1R,2R)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino}methyl)phenyl]amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-({2-ethyl-3-[(3-hydroxypiperidin-1-yl)methyl]phenyl}amino)-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{{2-ethyl-3-({[1-(hydroxymethyl)-2-methylpropyl]amino}methyl)phenyl]amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{{2-ethyl-3-({[4-(methylsulfonyl)benzyl]amino}methyl)phenyl]amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate

7-[(2-ethyl-3-{{(2-hydroxypropyl)amino}methyl}phenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethyl-3-{{(2-hydroxy-1-methylethyl)amino}methyl}phenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{{2-ethyl-3-(1H-imidazol-1-ylmethyl)phenyl]amino}-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate

7-[(3-{{(2,3-dihydroxypropyl)amino}methyl}-2-ethylphenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{{2-ethyl-3-(morpholin-4-ylmethyl)phenyl]amino}-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate

7-{{3-({[(1S)-1-benzyl-2-hydroxyethyl]amino}methyl)-2-ethylphenyl]amino}-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethyl-3-{{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}phenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-({2-ethyl-3-[(3-hydroxypyrrolidin-1-yl)methyl]phenyl}amino)-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{{2-ethyl-3-({[(1S)-2-hydroxy-1-phenylethyl]amino}methyl)phenyl]amino}-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethyl-3-{{[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]methyl}phenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{{2-ethyl-3-({[(1S,2S)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino}methyl)phenyl]amino}-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethyl-3-{{(2-hydroxycyclohexyl)amino}methyl}phenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

- 7-{{2-ethyl-3-({[(1R,2S)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino}methyl)phenyl]amino}-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-{{2-ethyl-3-({[(1R,2R)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino}methyl)phenyl]amino}-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-({2-ethyl-3-[(3-hydroxypiperidin-1-yl)methyl]phenyl}amino)-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-{{(2-hydroxypropyl)amino}methyl}phenyl)amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-{{(2-hydroxy-1-methylethyl)amino}methyl}phenyl)amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-{{2-ethyl-3-(1H-imidazol-1-ylmethyl)phenyl]amino}-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
- 7-[(3-{{(2,3-dihydroxypropyl)amino}methyl}-2-ethylphenyl)amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-{{2-ethyl-3-(morpholin-4-ylmethyl)phenyl]amino}-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide trifluoroacetate
- 7-{{3-({[(1S)-2-cyclohexyl-1-(hydroxymethyl)ethyl]amino}methyl)-2-ethylphenyl]amino}-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-{{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}phenyl}amino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-({2-ethyl-3-[(3-hydroxypyrrolidin-1-yl)methyl]phenyl}amino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-{{2-ethyl-3-({[(1S)-2-hydroxy-1-phenylethyl]amino}methyl)phenyl]amino}-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-{{(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]methyl}phenyl)amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-{{2-ethyl-3-({[(1S,2S)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino}methyl)phenyl]amino}-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-{{(2-hydroxycyclohexyl)amino}methyl}phenyl)amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-({2-ethyl-3-[(3-hydroxypiperidin-1-yl)methyl]phenyl}amino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

Pharmacological Data

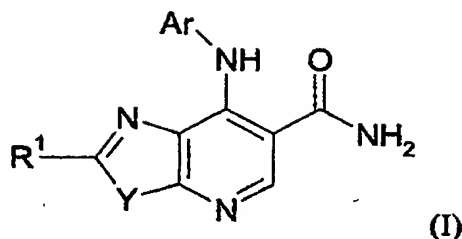
JAK3 HTRF assay

- 5 The JAK3 kinase assay utilizes a fusion protein (Jak3 kinase domain fused to Glutathione S-transferase, GST) coexpressed in E.Coli with GroEL/S, and purified by affinity chromatography on Glutathione Sepharose. The enzyme is diluted in 10 mM Tris-HCl, 150 mM NaCl, 5% mannitol, 2 mM 2-mercaptoethanol and 30% glycerol. The substrate in the kinase reaction is a biotinylated peptide of the autophosphorylation site of JAK3
- 10 (biotin-LPDKDYYVREPG) used at 2 μ M. Assay conditions are as follows: JAK3, compound and substrate are incubated in 25 mM Trizma base, 5 mM $MgCl_2$, 5 mM $MnCl_2$, 0.05% TritonX-100 and 2 μ M ATP for 45 min at RT. Reaction volume is 20 μ M. Stopsolution is added for a final concentration of 100 μ M EDTA. Finally 0.065 mg/ml PT66-K and 10.42 μ M SA-XL665 are added in 50 mM Hepes, 0.5 M KF and 0.1% BSA.
- 15 The plate is read in a Discovery instrument after 60 min incubation.

The compounds of the examples have an IC₅₀ less than 25 μ M

CLAIMS

1. A compound of formula (I):



wherein:

Y is NH, S or O;

R¹ is phenyl or a 5- to 7-membered heteroaromatic ring containing 1 to 3 heteroatoms, each of which is optionally substituted by one or more groups selected from C₁-C₈ alkyl, C₁-C₈ alkoxy, S(O)_nC₁-C₈ alkyl or a group -R²-(CH₂)_p-R³;

n is 0, 1 or 2;

R² is a bond, NH, NC₁-C₈ alkyl, S or O;

p is 0 - 3;

R³ is NR⁴R⁵ where R⁴ and R⁵ are independently hydrogen or C₁-C₈ alkyl, or R³ is a phenyl ring, a 5 to 7-membered saturated ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulphur, or a 5- to 7-membered heteroaryl group containing 1 to 3 heteroatoms selected from nitrogen oxygen and sulphur, each of which can optionally substituted by one or more groups selected from CONR⁴R⁵, NR⁴R⁵, C₁-C₈ alkyl, C₁-C₈ alkoxy, S(O)_nC₁-C₈ alkyl, hydroxyl, CN, halogen, NHCOC₁-C₈alkyl, R²-(CH₂)_p-OH or morpholine;

n is 1 to 4;

Ar is phenyl which can be optionally substituted by one or more groups selected from halogen, hydroxy, cyano, C₁-C₈ alkyl (itself optionally substituted by one or more hydroxy

or cyano groups or fluorine atoms), $\text{CH}_2\text{-R}^6$; $\text{CH}_2\text{O}(\text{CH}_2)_n\text{OC}_{1-6}$ alkyl, $\text{C}_1\text{-C}_8$ alkyl- $\text{NR}^3\text{-R}^4$, or a C_{2-6} alkyl chain optionally containing an NR^7 group in the chain and optionally substituted by one or more OH groups and optionally terminating in a cycloalkyl or phenyl group, the cycloalkyl and phenyl groups themselves being optionally substituted by one or more hydroxyl groups;

R^6 is a 5 to 7-membered saturated ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulphur, an aryl or 5- to 7-membered heteroaryl group containing 1 to 3 heteroatoms selected from nitrogen oxygen and sulphur, each of which can optionally substituted by one or more substituents selected from hydroxyl or hydroxymethyl;

R^7 is hydrogen or C_{1-6} alkyl;

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 in which NH or S.
3. A compound according to claim 1 or 2 in which R^1 is pyridyl or phenyl optionally substituted by SCH_3 , SOCH_3 , O-Ph-CONH_2 , $\text{NH}(\text{CH}_2)_3$ morpholine, $\text{O}(\text{CH}_2)_3\text{-N}(\text{CH}_3)_2$, $\text{O}(\text{CH}_2)_2$ morpholine, OCH_3 , $\text{O}(\text{CH}_2)_2\text{-N}(\text{CH}_3)_2$, 2-(3-aminophenoxy), 4-methoxyphenoxy, OH, $\text{N}(\text{CH}_3)_2$, OCH_3 , CN, fluoro, chloro, $\text{S}(\text{O})_2\text{CH}_3$, NHCOCH_3 , $\text{O}(\text{CH}_2)_2\text{OH}$, $\text{N}(\text{CH}_3)(\text{CH}_2)_2\text{OH}$, morpholine or $\text{O}(\text{CH}_2)_2\text{-OH}$.
4. A compound according to claim 1 or 2 in which the Ar is substituted by selected from hydroxymethyl, ethyl, [(2-hydroxypropyl)amino]methyl, [(2-hydroxy-1-methylethyl)amino]methyl, (1H-imidazol-1-yl)methyl, [(2,3-dihydroxypropyl)amino]methyl, 3-(morpholin-4-yl)methyl, {[2-cyclohexyl-1-(hydroxymethyl)ethyl]amino}methyl, {[1-benzyl-2-hydroxyethyl]amino}methyl, (3-hydroxypyrrolidin-1-yl)methyl, {[2-hydroxy-1-phenylethyl]amino}methyl, {[2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino}methyl, {(2-hydroxycyclohexyl)amino}methyl, {(2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino}methyl, 3-hydroxypiperidin-1-ylmethyl, {[1-(hydroxymethyl)-2-methylpropyl]amino}methyl, {[4-(methylsulphonyl)benzyl]amino}methyl, or {[2-(3,4-dihydroxyphenyl)-2-hydroxyethyl]amino}methyl.

5. A compound according to claim 1 which is:

7-{{3-(hydroxymethyl)-2-methylphenyl}amino}-2-(methylthio)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide

7-[(2-ethylphenyl)amino]-2-(methylsulfinyl)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide

5 2-[4-(aminocarbonyl)phenoxy]-7-[(2-ethylphenyl)amino][1,3]thiazolo[5,4-b]pyridine-6-carboxamide

7-[(2-ethylphenyl)amino]-2-[(3-morpholin-4-ylpropyl)amino][1,3]thiazolo[5,4-b]pyridine-6-carboxamide

10 2-[3-(dimethylamino)propoxy]-7-[(2-ethylphenyl)amino][1,3]thiazolo[5,4-b]pyridine-6-carboxamide

7-[(2-ethylphenyl)amino]-2-(methylthio)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide

7-[(2-ethylphenyl)amino]-2-(2-morpholin-4-ylethoxy)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide

7-[(2-ethylphenyl)amino]-2-methoxy[1,3]thiazolo[5,4-b]pyridine-6-carboxamide

15 7-[(2-methylphenyl)amino]-2-(methylthio)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide

2-[2-(dimethylamino)ethoxy]-7-[(2-ethylphenyl)amino][1,3]thiazolo[5,4-b]pyridine-6-carboxamide

2-(3-aminophenoxy)-7-[(2-ethylphenyl)amino][1,3]thiazolo[5,4-b]pyridine-6-carboxamide bis(trifluoroacetate)

20 7-[(2-ethylphenyl)amino]-2-(4-methoxyphenoxy)[1,3]thiazolo[5,4-b]pyridine-6-carboxamide

7-{{2-ethyl-3-(hydroxymethyl)phenyl}amino}-2-phenyl-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethylphenyl)amino]-2-(4-hydroxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

25 2-[4-(dimethylamino)phenyl]-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide bis(trifluoroa

7-[(2-ethylphenyl)amino]-2-(3-hydroxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethylphenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-

30 carboxamide 2-(3,4-dihydroxyphenyl)-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide

2-(3-cyanophenyl)-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide

2-(4-cyanophenyl)-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethylphenyl)amino]-2-(4-hydroxy-3-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

35 2-(3,4-difluorophenyl)-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide

2-(3-chloro-4-hydroxyphenyl)-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethylphenyl)amino]-2-(1H-imidazol-4-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethylphenyl)amino]-2-[4-(methylsulfonyl)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

2-[4-(acetyl amino)phenyl]-7-[(2-ethylphenyl)amino]-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethylphenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethylphenyl)amino]-2-{4-[(2-hydroxyethyl)(methyl)amino]phenyl}-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethylphenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethylphenyl)amino]-2-phenyl-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{[2-ethyl-3-(hydroxymethyl)phenyl]amino}-2-(4-hydroxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{[2-ethyl-3-(hydroxymethyl)phenyl]amino}-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethylphenyl)amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethylphenyl)amino]-2-pyridin-3-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide 7-[(2-ethylphenyl)amino]-2-pyridin-2-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

2-[4-(2-{[tert-butyl(diphenyl)silyl]oxy}ethoxy)phenyl]-7-{[2-ethyl-3-(hydroxymethyl)phenyl]amino}-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{[2-ethyl-3-(hydroxymethyl)phenyl]amino}-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{[2-ethyl-3-(hydroxymethyl)phenyl]amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethyl-3-{[(2-hydroxypropyl)amino]methyl}phenyl)amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethyl-3-{[(2-hydroxypropyl)amino]methyl}phenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethyl-3-{[(2-hydroxy-1-methylethyl)amino]methyl}phenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{[2-ethyl-3-(1H-imidazol-1-ylmethyl)phenyl]amino}-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide

- 7-[(3-[(2,3-dihydroxypropyl)amino]methyl)-2-ethylphenyl]amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[[2-ethyl-3-(morpholin-4-ylmethyl)phenyl]amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 5 7-[[3-([(1S)-2-cyclohexyl-1-(hydroxymethyl)ethyl]amino)methyl]-2-ethylphenyl]amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[[3-([(1S)-1-benzyl-2-hydroxyethyl]amino)methyl]-2-ethylphenyl]amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 10 7-[(2-ethyl-3-[[4-(2-hydroxyethyl)piperazin-1-yl]methyl]phenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-[(3-hydroxypyrrolidin-1-yl)methyl]phenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[[2-ethyl-3-([(1S)-2-hydroxy-1-phenylethyl]amino)methyl]phenyl]amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 15 7-[(2-ethyl-3-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]methyl]phenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[[2-ethyl-3-([(1S,2S)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino)methyl]phenyl]amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 20 7-[(2-ethyl-3-[(2-hydroxycyclohexyl)amino]methyl]phenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[[2-ethyl-3-([(1R,2S)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino)methyl]phenyl]amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 25 7-[[2-ethyl-3-([(1R,2R)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino)methyl]phenyl]amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-[(3-hydroxypiperidin-1-yl)methyl]phenyl)amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 30 7-[[2-ethyl-3-([1-(hydroxymethyl)-2-methylpropyl]amino)methyl]phenyl]amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[[2-ethyl-3-([4-(methylsulfonyl)benzyl]amino)methyl]phenyl]amino]-2-[4-(2-hydroxyethoxy)phenyl]-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 35 7-[[3-([(2-(3,4-dihydroxyphenyl)-2-hydroxyethyl]amino)methyl]-2-ethylphenyl]amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

- 7-[(2-ethyl-3-[(2-hydroxypropyl)amino]methyl)phenyl]amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-[(2-hydroxy-1-methylethyl)amino]methyl)phenyl]amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 5 7-[[2-ethyl-3-(1H-imidazol-1-ylmethyl)phenyl]amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(3-[(2,3-dihydroxypropyl)amino]methyl)-2-ethylphenyl]amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[[2-ethyl-3-(morpholin-4-ylmethyl)phenyl]amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 10 7-[[3-([(1S)-2-cyclohexyl-1-(hydroxymethyl)ethyl]amino)methyl]-2-ethylphenyl]amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[[3-([(1S)-1-benzyl-2-hydroxyethyl]amino)methyl]-2-ethylphenyl]amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 15 7-[(2-ethyl-3-[[4-(2-hydroxyethyl)piperazin-1-yl]methyl]phenyl]amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide 7-[(2-ethyl-3-[(3-hydroxypyrrolidin-1-yl)methyl]phenyl]amino)-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[[2-ethyl-3-([(1S)-2-hydroxy-1-phenylethyl]amino)methyl]phenyl]amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 20 7-[(2-ethyl-3-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]methyl]phenyl]amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[[2-ethyl-3-([(1S,2S)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino)methyl]phenyl]amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 25 7-[(2-ethyl-3-[(2-hydroxycyclohexyl)amino]methyl)phenyl]amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[[2-ethyl-3-([(1R,2S)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino)methyl]phenyl]amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 30 7-[[2-ethyl-3-([(1R,2R)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino)methyl]phenyl]amino]-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 7-[(2-ethyl-3-[(3-hydroxypiperidin-1-yl)methyl]phenyl]amino)-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide
- 35

7-{{2-ethyl-3-({[1-(hydroxymethyl)-2-methylpropyl]amino}methyl)phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{{2-ethyl-3-({[4-(methylsulfonyl)benzyl]amino}methyl)phenyl}amino}-2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

5 7-[(2-ethyl-3-{{(2-hydroxypropyl)amino}methyl}phenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethyl-3-{{(2-hydroxy-1-methylethyl)amino}methyl}phenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

10 7-{{2-ethyl-3-(1H-imidazol-1-ylmethyl)phenyl}amino}-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(3-{{(2,3-dihydroxypropyl)amino}methyl}-2-ethylphenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{{2-ethyl-3-(morpholin-4-ylmethyl)phenyl}amino}-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

15 7-{{3-({[(1S)-1-benzyl-2-hydroxyethyl]amino}methyl)-2-ethylphenyl}amino}-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethyl-3-{{4-(2-hydroxyethyl)piperazin-1-yl}methyl}phenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

20 7-((2-ethyl-3-{{(3-hydroxypyrrolidin-1-yl)methyl}phenyl}amino)-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{{2-ethyl-3-({[(1S)-2-hydroxy-1-phenylethyl]amino}methyl)phenyl}amino}-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethyl-3-{{(2R)-2-(hydroxymethyl)pyrrolidin-1-yl}methyl}phenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

25 7-{{2-ethyl-3-({[(1S,2S)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino}methyl)phenyl}amino}-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethyl-3-{{(2-hydroxycyclohexyl)amino}methyl}phenyl)amino]-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

30 7-{{2-ethyl-3-({[(1R,2S)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino}methyl)phenyl}amino}-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-{{2-ethyl-3-({[(1R,2R)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino}methyl)phenyl}amino}-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide)

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7-({2-ethyl-3-[(3-hydroxypiperidin-1-yl)methyl]phenyl} amino)-2-(4-morpholin-4-ylphenyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethyl-3-[(2-hydroxypropyl)amino]methyl}phenyl)amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

5 7-[(2-ethyl-3-[(2-hydroxy-1-methylethyl)amino]methyl}phenyl)amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethyl-3-(1H-imidazol-1-yl)methyl}phenyl)amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

10 7-[(3-[(2,3-dihydroxypropyl)amino]methyl}-2-ethylphenyl)amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethyl-3-(morpholin-4-ylmethyl)phenyl)amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(3-[(1S)-2-cyclohexyl-1-(hydroxymethyl)ethyl]amino}methyl)-2-ethylphenyl]amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

15 7-[(2-ethyl-3-[(4-(2-hydroxyethyl)piperazin-1-yl)methyl}phenyl)amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-({2-ethyl-3-[(3-hydroxypyrrolidin-1-yl)methyl]phenyl} amino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

20 7-[(2-ethyl-3-[(1S)-2-hydroxy-1-phenylethyl]amino}methyl)phenyl]amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-[(2-ethyl-3-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl)methyl}phenyl)amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

25 7-[(2-ethyl-3-[(1S,2S)-2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino}methyl)phenyl]amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide)

7-[(2-ethyl-3-[(2-hydroxycyclohexyl)amino]methyl}phenyl)amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

7-({2-ethyl-3-[(3-hydroxypiperidin-1-yl)methyl]phenyl} amino)-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

30 7-[(2-ethyl-3-[(1-(hydroxymethyl)-2-methylpropyl)amino}methyl)phenyl]amino]-2-pyridin-4-yl-3H-imidazo[4,5-b]pyridine-6-carboxamide

or a pharmaceutically acceptable salt thereof.

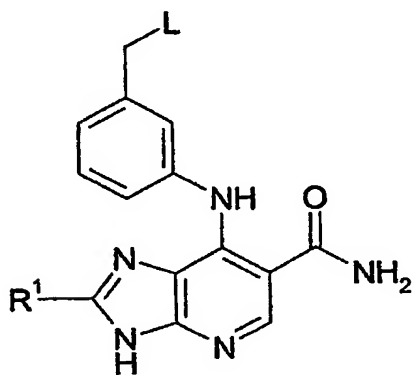
6. A compound of formula (I) as defined in any one of claims 1 to 5 for use in therapy

7. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier.

8. A method of treating a disease or condition mediated by JAK3 which comprises administering to a patient in need of such treatment a compound of formula (I) as defined in claims 1 to 5 or a pharmaceutically acceptable salt thereof.

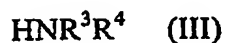
9. A method according to claim 8 in which the disease or condition is asthma, host versus graft rejection/transplantation or rheumatoid arthritis.

10. A process for the preparation of a compound of formula (I) which comprises:
(a) for compounds of formula (I) where Y is NH and Ar is phenyl substituted by $\text{CH}_2\text{NR}^3\text{R}^4$, reaction of a compound of formula (II):



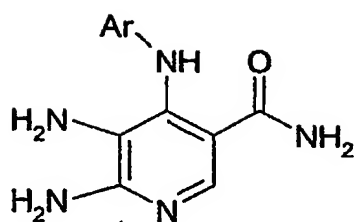
(II)

in which R^1 is as defined in formula (I) or is a protected derivative thereof and L is a leaving group, with a compound of formula (III):



in which R^3 and R^4 are as defined in formula (I) or are protected derivatives thereof, or

(b) for compounds of formula (I) where Y is NH, reaction of a compound of formula (IV):



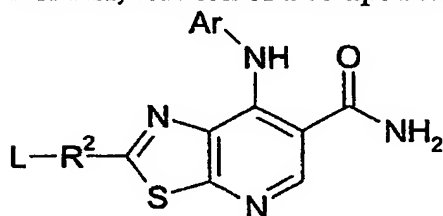
(IV)

- 5 in which Ar is as defined in formula (I) or is a protected derivative thereof, with a compound of formula (V):



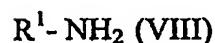
- 10 in which R^1 is as defined in formula (I) or is a protected derivative thereof, or

(c) for compounds of formula (I) where Y is S and R^1 is a group $-R^2\text{-(CH}_2\text{)}_p\text{-R}^3$ where R^2 is O or NH, reaction of a compound of formula (VI):



(VI)

15 in which Ar is as defined in formula (I) or is a protected derivative thereof, R^2 is O or NH, and L is a leaving group, with a compound of formula (VII) or (VIII):



- 20 in which R^1 is as defined in formula (I) or is a protected derivative thereof

and optionally thereafter any of the above processes:

- removing any protecting groups

Patent 05.00

- converting a compound of formula (I) into a further compound of formula (I)
- forming a pharmaceutically acceptable salt.

Patent 05.00

ABSTRACT

5 The present invention relates to novel imidazo and thiazolopyridine compounds which are
JAK3 Kinase inhibitors, methods for their preparation intermediates and pharmaceutical
compositions comprising them.

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